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Numerical Simulation of Red Blood Cells' Motion, A Review

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Abstract

The microcirculation of blood plays an important role in human body by providing oxygen and nutrients to the cells and removing carbon dioxide and wastes from the cells. This process is greatly affected by the rheological properties of the Red Blood Cells (RBCs). Changes in the rheological properties of the RBCs are caused by certain human diseases such as malaria and sickle cell diseases. Therefore it is important to understand the motion and deformation mechanism of RBCs in order to diagnose and treat this kind of diseases. Although, many methods have been developed to explore the behaviour of the RBCs in microchannels, they could not explain the deformation mechanism of the RBCs properly. Recently developed Particle Methods are employed to explain the RBCs' behaviour in microchannels more comprehensively. The main objective of this study is to critically analyze the present methods, used to model the RBC behaviour in microchannels, in order to develop a computationally efficient particle based model to describe the complete behaviour of the RBCs in microchannels accurately and comprehensively.

Keywords: Red Blood Cells, RBCs, Erythrocytes, Microcirculation, Simulation, Biomechanical.

Introduction

It is commonly accepted that the blood is a non-Newtonian and inhomogeneous fluid (Pontrelli, 1998; Wada & Nakamura, 2008). Blood can be considered as a suspension of different blood cells; Red Blood Cells (erythrocytes), White Blood Cells (leukocytes) and Platelets (thrombocytes), in a fluid, called plasma which is composed mainly of water. Among all the blood cells more than 99% of blood cells are RBCs and they occupy about 45% of total blood volume (Skalak, Ozkaya & Skalak, 1989; Tsubota, Wada & Yamaguchi, 2006a). The healthy human RBCs have a biconcave disk shape (Figure 1) with a mean diameter of about $8\mu\text{m}$ and a mean thickness of about $2\mu\text{m}$ at rest. The average surface area and the average volume of a normal RBC are $135\mu\text{m}^2$ and $90\mu\text{m}^3$ respectively (Shi, Pan & Glowinski, 2012). Human RBCs are nonnucleated deformable liquid capsules (Pozrikidis, 2003) enclosed by a thin viscoelastic membrane, which consists of a lipid bilayer supported by a mesh-like cytoskeleton, formed by a network of spectrin proteins linked by short filaments of actin (Fedosov, Caswell & Karniadakis, 2010; Pozrikidis, 2003). This biological membrane contains an incompressible Newtonian fluid called cytoplasm, which contains large amount of haemoglobin and they are highly efficient at binding oxygen (Korin, Bransky & Dinnar, 2007).

Blood continuously flows within the cardiovascular network, as blood flows from heart to arteries, capillaries, veins and then flows back to the heart. Heart pumps oxygen rich blood to tissues and the organs of the body through arteries. In the tissues, blood moves through the capillaries, which are the smallest blood vessels in the body, in where haemoglobin of RBCs releases oxygen to the cells

and absorbs carbon dioxide from cells. Carbon dioxide rich blood then travels through the veins to the heart, which pumps the blood to the lungs. In the lungs, haemoglobin absorbs oxygen from air and releases carbon dioxide, due to the high concentration of oxygen of air in lungs. Finally, blood moves back to the heart. There are about 10^{10} blood vessels, whose diameters are in the range of 5-10 μm , (Dzwinel, Boryczko & Yuen, 2003). In the capillary vessels, RBCs reveal a number of interesting shapes and dynamics in response to the flow conditions, which are crucial for optimal mass transfer. The importance of understanding the mass transfer, such as oxygen and carbon dioxide exchange between the RBCs and tissues through capillaries, motivated a number of experimental (in vivo and in vitro), theoretical and numerical studies.

Previous studies on Microcirculation and RBCs

Experimental studies

The invention of microscope in the seventeenth century, led to discover the network of capillaries in the human body. In 1830, Poiseuille conducted number of experiments using liquids and cylindrical tubes, which contributed to understand the blood flow in the large vessels and in the microcirculation (Popel & Johnson, 2005). Fahraeus observed that the average RBCs concentration in the blood flow decreases when the capillary diameter decreases below 300 μm (Pozrikidis, 2005a). As a result, discharge hematocrit (overall volume fraction of RBCs) is greater than the tube hematocrit (volume fraction of RBCs inside the capillary). This behavior is known as Fahraeus effect. Furthermore, Fahraeus reported that the apparent viscosity of the blood decreases in the blood vessels having diameter in between 8 μm to 500 μm . Further decrease in capillary diameter shows a rapid increase of apparent viscosity, which is known as Fahraeus-Lindqvist effect (Bagchi, 2007). In order to understand the RBCs deformation and different rheological properties, a number of experiments have been conducted with the aid of optical tweezers (Dao, Lim & Suresh, 2003), Micropipette aspiration (Artmann et al., 1997), and optical magnetic twisting cytometry (Fedosov et al., 2010).

Many researchers reported three different types of RBCs motions (Figure 3) in a linear shear flow, namely, tank treading, tumbling, and vacillating breathing (Danker, Verdier & Misbah, 2008; Shi et al., 2012; Veerapaneni, Young, Vlahovska & Bławdziewicz, 2011). For higher shear rates and higher viscosities of plasma, RBCs show tumbling motion, in which the RBCs undergo flipping motion while hardly change their shapes. On the other hand, for the lower plasma viscosities or lower shear rates, RBCs deform into ellipsoidal shapes with constant inclined angles, while the membrane circulates around the cytoplasm, which is known as tank treading motions (Keller & Skalak, 1982). Depending on the degree of confinement and the maximum flow velocity the vacillating breathing motion of RBCs can be seen, in which the major axis of the RBC oscillates around the shear direction accompanied with breathing like motion (Shi et al., 2012; Vitkova, Mader, Polack, Misbah & Podgorski, 2008). Furthermore, in a Poiseuille flow, three different shapes of RBCs including Parachute shape, bullet-like shape and slipper shape can be found in literature, depending on the rheological properties of the RBCs and flow conditions (Hosseini & Feng, 2009; Kaoui, Biros & Misbah, 2009). Since it is difficult to study the microcirculation and rheological properties of RBCs quantitatively, due to the micro sized dimensions, most recent researches are conducted based on the numerical modelling.

Numerical studies

In last few decades, a number of numerical models have been introduced to study the RBCs behaviour in blood vessels. Pozrikidis (Pozrikidis, 2003) developed a numerical model based on the Boundary Element Method (BEM) to simulate the RBCs motion in a Poiseuille flow. Pozrikidis revealed that diskoidal RBCs, initially placed at the major axis of the capillary tube achieve an axisymmetric parachute shape as RBCs advance the capillary tubes, while the RBCs placed intermediate orientation angles attain a slipper-like shapes (Pozrikidis, 2005b). But in the BEM, flow is restricted on a Stokes flow region. Therefore, it is not possible to extend the simulation for large vessels, where the temporal unsteady effect should be considered (Ii, Sugiyama, Takagi & Matsumoto, 2012). Sun and Munn (Sun & Munn, 2005) employed the Lattice Boltzmann approach to simulate the two-dimensional blood flow in a blood vessel, considering blood cells as a suspension of blood cells in plasma. They reproduced the motion of blood cells in plasma to explain the experimental results, such as Fahraeus-Lindqvist effect and Fahraeus effect (Sun & Munn, 2005). However, in this model the deformation characteristics of the RBCs were ignored, since all the blood cells were modelled as rigid bodies (Tsubota, Wada & Yamaguchi, 2006b).

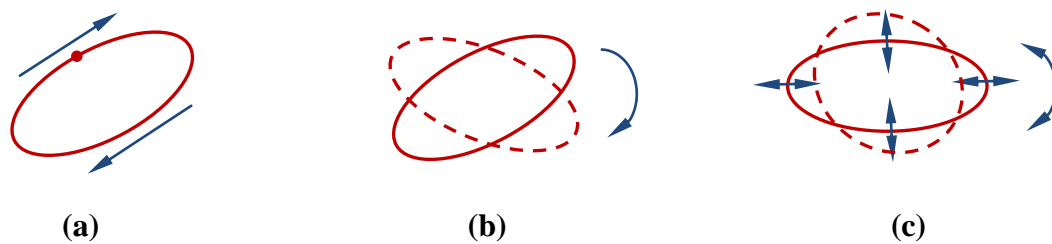


Figure 1. Three motions of RBCs (a) Tank Treading (b) Tumbling (c) Vacillating Breathing

Eggleton and popel (Eggleton & Popel, 1998) used the Immersed Boundary Method (IBM) to simulate the deformation of a capsule in a simple shear flow and revealed that the RBC membrane shows an asymptotic behaviour as the ratio between the dilation modulus to extensional modulus is increased. However, the capsule response was followed for short time (Sui, Chew, Roy & Low, 2008). Shi et al. employed IBM to study the deformation of single RBC in Poiseuille flow and found that the RBCs tend to move towards the axis of the microvessel (Shi et al., 2012). Further, they stated that the steady state shape of the RBCs in Poiseuille flow depends on the swelling ratio, initial inclined angle of the RBC, maximum velocity of the Poiseuille flow, the height of the capillary, and the bending stiffness of the RBC membrane. In addition, the same method has been used by Takagi et al. (Takagi, Yamada, Xiaobo & Matsumoto, 2009) to analyse the deformation of blood cells.

The above methods divide the continuum materials into discrete elements and the individual elements are interconnected by a topological map, known as a mesh or grid. Then a suitable interpolation function is built upon the mesh (Ii et al., 2012; Tsubota, Wada, Kamada, et al., 2006) and solutions are obtained by solving partial differential equations. However, this approach cannot be used with complex geometries and multiphysics problems. Further, these studies have been conducted without considering the influence of the rheological properties of the intercellular fluid on the deformation mechanism of the RBCs and they have not addressed the inhomogeneous nature of the RBCs. To understand the RBCs behaviour in microchannels more accurately, it is essential to develop models, which can capture and describe more subcellular details, such as RBC

wall and cytoplasm interactions and the differences in the RBCs shapes and sizes (Van Liedekerke et al., 2010).

Recently developed particle methods can be used to model RBCs motion and deformation in microchannels with more subcellular details. These methods directly address the inhomogeneous nature of the blood flow and they can be used to simulate single and multi phase fluid dynamics. Using particle methods, it is convenient to model the internal structure of the blood cells. A two-dimensional model was presented by Tanaka and Takano (Tanaka & Takano, 2005) using Smoothed Particle Hydrodynamics (SPH) to demonstrate the tank treading behaviour of a single RBC under shear flow and the axial migration of RBCs under Poiseuille flow. In this model both Plasma and cytoplasm were discretized into fluid particles in the SPH sense while the RBC membrane was discretized into solid particles, which were interconnected by elastic springs. The forces act on the RBC membrane was calculated by the pressure difference between the plasma and the cytoplasm. While the forces acting on the fluid particles, by the membrane particles, were calculated by the interaction forces based on the SPH method. Then the system was mathematically modelled by the Navier-Stokes equations with the external forces. They recognised that cytoplasm viscosity makes a significant contribution for the deformation of RBC membrane. But the simulated results showed a significant disagreement with the experimental results, due to the use of less number of particles to represent the RBCs membrane (Tanaka & Takano, 2005). Further, they emphasised that there might be mismatches between the experimental results and the analytical results, if the two-dimensional simulations were carried out.

Tsubota et al. (Tsubota, Wada, Kamada, et al., 2006; Tsubota, Wada, et al., 2006a, 2006b) analysed the motion and the deformation of a RBC, using Moving Particle Semi-implicit (MPS) method. The RBC membrane and the Plasma were discretized into particles and the membrane particles were interconnected to the neighbouring particle by the elastic springs as shown in Fig.1 This RBC model consider the elastic energy stored in the springs due to the stretch/ compression is given by Eq. (1) and the elastic bending energy stored in the springs due to the bending is given by Eq. (2). Energy associated with the incompressibility of the RBC membrane can be expressed by Eq. (3). The total energy of the RBC membrane is the sum of the above energies, $E=E_l+E_b+E_s$.

$$E_l = \frac{1}{2} K_l \sum_{i=1}^N \left(\frac{l_i - l_0}{l_0} \right)^2 \quad (1)$$

$$E_b = \frac{1}{2} K_b \sum_{i=1}^N \tan^2 \left(\frac{\theta_i}{2} \right) \quad (2)$$

$$E_s = \frac{1}{2} K_s \left(\frac{s - s_e}{s_e} \right)^2 \quad (3)$$

$$\mathbf{F}_i = - \frac{\partial E}{\partial \mathbf{r}_i} \quad (4)$$

$$m_i \ddot{\mathbf{r}}_i + \gamma \dot{\mathbf{r}}_i = \mathbf{F}_i \quad (5)$$

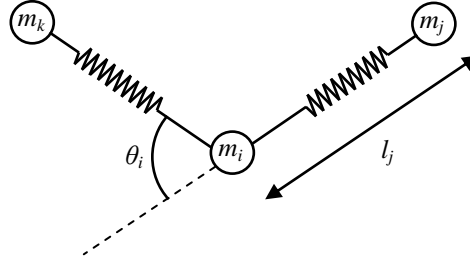


Figure 2. Spring network model of the RBC

Where E is the total energy, l_0 is the reference length between pair of consecutive RBC particles (i and $i+1$) and s_e is the equivalent area of the RBC membrane, while l_i , θ_i , and s are the length of the springs, angle between pair of consecutive springs and area of the RBC membrane respectively. K_l , K_b and K_s are the energy constants. The forces acting on each membrane particle are calculated based on the principal of virtual work. (Eq. (4)). The initial shape of the RBC at rest is obtained, as total energy is minimized. Finally the motion of the RBC membrane particles is modeled by the Eq. (5), where the m_i and γ is the mass and membrane viscosity of each RBC membrane particle. However, two-dimensional simulation of the blood flow represents rather qualitative results on the motion and the deformation of the RBCs. In addition, the formation of a blood clot, due to the aggregation of platelets, was modelled. To analyse the aggregation of platelets each platelet was modelled by a single particle. Imani et al. (Imai et al., 2009) developed a three-dimensional numerical model to simulate the Malaria Infected Red Blood Cell (IRBC). In their model, all the components of the blood are modelled by discrete particles, while the Malaria parasites inside the RBCs are represented by cluster of rigid particles. For this simulation, the biconcave shaped healthy RBC and the spherical shaped of IRBC are used, as the IRBCs become more stiffer and less deformable, to qualitatively examine the flow in a narrow 6 square channel. Results revealed that IRBC cannot flow through the narrow channels (Imai et al., 2009). Hosseini and Feng (Hosseini & Feng, 2009) proposed a two-dimensional particle based model, in which plasma and cytoplasm were discretized into the particles in Smoothed Particle Hydrodynamics (SPH) procedure. Initial biconcave shape of the RBC membrane at rest is obtained by the widely used geometrical function (Eq. 5). Where $R_0=3.91\mu\text{m}$, $C_0= 0.02072$, $C_1=2.00256$, $C_2= -1.1228$ and $R^2= (X^2+Y^2) / R_0^2 \leq 1$. When $Y=0$, the two-dimensional biconcave shape of the RBC can be derived.

$$Z= \pm 0.5R_0 [1- R^2]^{0.5}[C_0+C_1R^2 +C_2R^4] \quad (5)$$

Under the assumption that both plasma and cytoplasm have the same viscosity, tank treading motion of the RBCs in the simple shear flow and RBCs' parachute shape in Poiseuille flow were observed. But the initial biconcave shape of RBC membrane at rest used in this approach shows a significant mismatch with the initial shape obtained based on principal of virtual work (Fig. 3). Tosenberger et al. (Tosenberger, Salnikov, Bessonov, Babushkina & Volpert, 2011) compared the applicability of Molecular Dynamics (MD) and Dissipative Particle Dynamics (DPD) to model RBC motion in microvessels and noted that DPD model converges faster to a stable flow. Furthermore, they reported the bending coefficient of the RBC membrane greatly affects the RBC deformability.

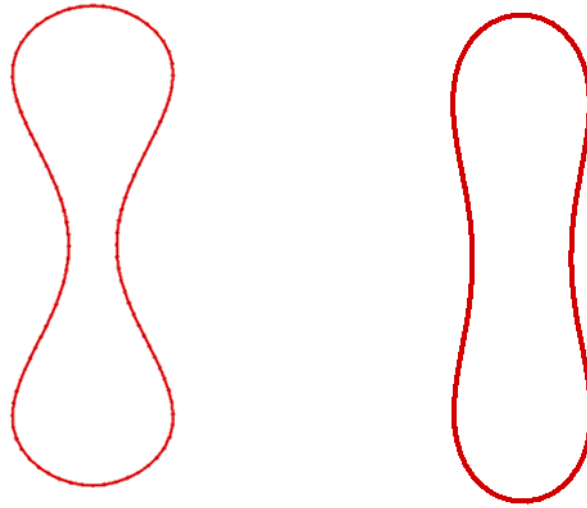


Figure 3. (a) Initial shape of the RBC by geometrical function (b) Initial shape of the RBC by minimum energy approach

Fedsov et al. (Fedosov et al., 2010) confirmed that the shape deformation decreases for larger values of RBC membranes bending rigidity and the simulation results revealed that the RBC membrane viscosity is 0.02-0.06 Pa.s, with respect to the cytoplasm viscosity of $\eta_i = 5 \times 10^{-3}$ Pa.s and plasma viscosity of $\eta_o = 1 \times 10^{-3}$ Pa.s. A modified MPS method was introduced by Ahmadian et al. (Ahmadian, Firoozbakhsh & Hasanian, 2012) to investigate the motion of the RBC through microvessels. Proposed method reduced the computational time by more than a factor of twenty without affecting the accuracy of the results. Recently a three-dimensional model was proposed by Nagayama and Honda (Nagayama & Honda) to simulate the RBC behaviour in the capillary blood flow using MPS method. But instead of solving Navier-Stokes equations, which were used in the above particle methods, a momentum equation for the RBC was developed, considering the inter-particle force, viscous diffusion and external force. Results show that the RBCs can have three types of shapes, depending on the internal diameter of the microvessel and tube hematocrit. Further, they studied the motion of RBCs in bent channels. But the complete RBC behaviour in microchannels was not explained by this model.

Conclusion

Though a number of models have been developed to describe the RBC behaviour in microchannels, the models developed based on the grid generation methods such as Boundary Element Method (BEM), and Immersed Boundary Method (IBM) have several limitations (Tsubota, Wada, Kamada, et al., 2006; Tsubota, Wada, et al., 2006b) compared with the recently developed meshfree particle methods. Constructing a regular grid for complex geometry such as for RBC is very time consuming task and these methods cannot handle large deformations of RBCs. Further, subcellular details, such as RBC wall and cytoplasm interactions cannot be completely included for the simulation. To overcome these limitations, several meshfree particle based models have been proposed to analyse the RBC behaviour in microchannels.

In the literature several particle methods can be found, such as Smoothed Particle Hydrodynamics (SPH), Dissipative Particle Dynamics (DPD), and Moving Particle Semi-implicit (MPS) method, which have been used to analyse RBCs motion and deformation. However, very few three-dimensional particle based models have been developed to simulate RBCs behaviour in microchannels. But three-dimensional models should be studied in order to capture more information of RBC deformation in microvessels accurately. Further, existing three-dimensional particle based models, have not consider the influence of internal fluid (cytoplasm) of the RBC,

though the influence of the cytoplasm is significant on the RBCs deformation (Tanaka & Takano, 2005). Therefore, using particle methods three-dimensional RBC model should be studied, considering the effect of RBCs interior fluid, in order to accurately investigate and predict the motion and the deformation mechanism in microvessels. Since Smoothed Particle Hydrodynamics (SPH) method has some unique advantages as a particle method over the conventional grid based methods (Liu & Liu, 2003), SPH method can be used to investigate the RBCs behaviour accurately, in microchannels.

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